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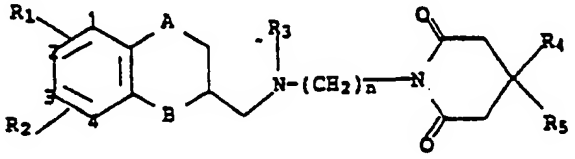

(I)

(57) Abstract

The present invention is directed to the use of a compound of formula (I), in which R_1 and R_2 each independently are represented by hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, nitro, hydroxy, SO_3H, SO_2NH_2, or R_1 and R_2 together may form a fused phenyl ring at the 1,2 or 3,4 positions, with the proviso that when R_1 and R_2 are identical, they represent hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, or halogen; A and B independently represent oxo, thio, or an imino group having the formula $-N(R_6)-$, wherein the group R_6 is represented by hydrogen or C_{1-4} alkyl; R_3 is hydrogen, C_{1-4} alkyl, or hydroxyethyl; n is represented by an integer from 2-5; and R_4 and R_5 are each represented by methyl or together form a cyclopentane or cyclohexane ring; the enantiomers thereof, and the pharmaceutically acceptable acid additon salts thereof, in the preparation of a medicament for the treatment of glaucoma.

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METHOD FOR THE TREATMENT OF GLAUCOMA

The present invention is directed to a method for the treatment of glaucoma. Another aspect of this invention is directed to new ophthalmic preparations which are useful in the treatment of glaucoma.

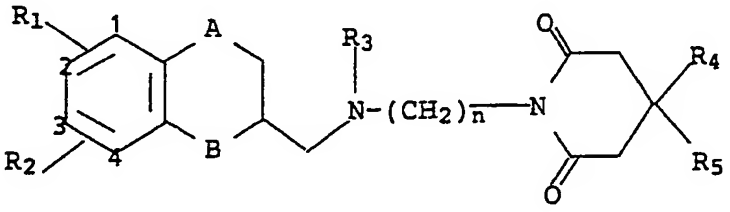
Glaucoma is a disorder in which elevated intraocular pressure damages the optic nerve thereby producing blindness. The are two major types of glaucoma, chronic open-angle and acute narrow-angle.

Intraocular pressure is controlled by the dynamics of aqueous humor. The aqueous humor is derived from blood by a process of secretion and ultrafiltration in the ciliary body. Aqueous humor then passes from the posterior chamber of the eye, through the pupil to fill the anterior chamber, which is the space between the back of the cornea and the plane of the iris and pupil. The aqueous humor is reabsorbed through the trabecular meshwork, located in the angle between the cornea and the iris. The aqueous humor then enters the canal of Schlemm so that it may be drained away from the eye.

In chronic open-angle glaucoma, the most common type, a defect in aqueous humor reabsorption exists at the level of the trabecular meshwork. Intraocular pressure rises above its normal maximum of 21 mm HG due to the presence of excess

aqueous humor. In acute narrow-angle glaucoma, dilation of the iris leads to the physical blockade of the entrance to the canal of Schlemm and a resulting excess of aqueous humor.

In accordance with the present invention, it has been discovered that these types of glaucoma can be treated by the administration of an effective amount one of the following compounds:



in which R_1 and R_2 each independently are represented by hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, nitro, hydroxy, SO_3H, SO_2NH_2, or R_1 and R_2 together may form a fused phenyl ring at the 1,2 or 3,4 positions, with the proviso that when R_1 and R_2 are identical, they represent hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, or halogen; A and B independently represent oxo, thio, or an imino group having the formula $-N(R_6)-$, wherein the group R_6 is represented by hydrogen or C_{1-4} alkyl; R_3 is hydrogen, C_{1-4} alkyl, or hydroxyethyl; n is represented by an integer from 2-5; and R_4 and R_5 are each represented by methyl or together form a cyclopentane or cyclohexane ring; the enantiomers thereof, and the pharmaceutically acceptable acid addition salts thereof.

As used in this application:

a) The term "C_{1-4} alkyl" refers to a straight chain or branched alkyl group containing up to 4 carbon atoms. Representative examples of suitable alkyl groups include, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl;

b) The term "halogen" refers to a fluorine, bromine, chlorine or iodine atom;

c) The term "C_{1-4}" alkoxy refers to a straight chain or branched alkoxy group containing up to 4 carbon atoms. Representative examples of suitable alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy;

d) The term "patient" as used herein is taken to mean warm-blooded animals, such as mammals, for example, dogs, rats, mice, cats, guinea pigs, horses, cattle, sheep and primates, including humans, and;

e) The term "glaucoma" should be construed as referring to either chronic open angle glaucoma or acute narrow angle glaucoma.

The expression "pharmaceutically acceptable acid addition salts" is intended to apply to any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acid and acid metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di- and tri-carboxylic acids.

Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicyclic, 2-phenoxybenzoic and sulfonic acids such as methane sulfonic acid and 2-hydroxyethane sulfonic acid.

Some of the compounds represented by Formula I exist as enantiomers. Any reference in this application to the compounds of Formula I, is meant to encompass a specific enantiomer or a racemic mixture.

Preferred compounds are those in which A and B are oxo, R_1, R_2, and R_3 are hydrogen, n is either 2 or 4 and R_4 and R_5 together form a cyclopentane ring. These compounds are 8-[2-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]-ethyl]-8-azaspiro[4,5]decane-7,9-dione and 8-[2-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]butyl]-8-azaspiro-[4,5]decane-7,9-dione.

The compounds of Formula I as well as their methods of preparation are known in the art. For example, see United States Patent No. 4,612,312, which is hereby incorporated by reference. The compounds are also known in the art as serotonin $5HT1_A$ antagonists.

It has been discovered that the compounds of Formula I decrease intraocular pressures and are therefore useful in the treatment of glaucoma. The exact mechanism by which these compounds decrease intraocular pressure is not fully understood. However it has been learned that these compounds produce constriction of the sphincter muscle of the iris. Constriction of this musale produces miosis (ie. constriction of the pupil). Several other drugs which are

known to be useful in the treatment of glaucoma also produce this effect upon the sphincter muscle of the iris. These drugs include pilocarpine, physostigmine, and echothiphate.

In acute narrow angle glaucoma, the iris physically blocks the entrance to the Canal of Schlemm. Contraction of the sphincter muscle of the iris ends this physical blockade and allows the outflow of aqueous humor from the eye. In chronic open angle glaucoma, there is no direct blockade of the Canal of Schlemm, rather there is a defect in the manner in which the trabeculae meshwork reabsorbs the aqueous humor. Contraction of the sphincter muscle of the iris improves the reabsorption of aqueous humor through the trabeculae meshwork into the Canal of Schlemm.

If desired, the compounds of Formula I can be administered systemically in order to lower intraocular pressures. They can be administered either orally or parenterally. The quantity of compound required to produce this anti-glaucoma effect will vary widely depending upon the particular compound utilized, the patient, the route of administration, the severity of the patient's glaucoma, the presence of other underlying disease states in the patient, and other medications which are being administered concurrently to the patient. Generally though, if the compounds are being administered systemically, than a patients' glaucoma will respond to a dosage range of from about 0.1 mg/kg/ day to about 100 mg/kg/day. This dosage will typically be administered from 1 to 4 times daily.

The compounds of Formula I can be compounded into a variety of systemic dosage forms, such as for example, tablets, capsules, solutions, elixirs, sterile solutions for injection and sustained release preparations. Methods

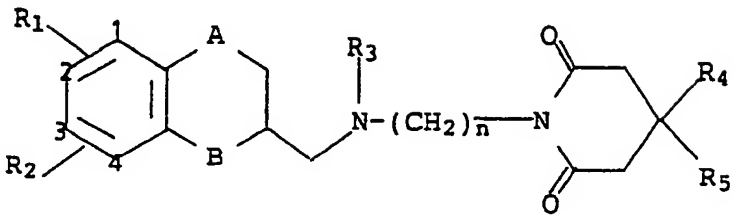
for producing these dosage forms are well known in the art and are disclosed in United States Patent No. 4, 612, 312.

The compounds can also be administered topically via ophthalmic dosage forms such as, for example, ophthalmic drops, ophthalmic ointments, and ophthalmic disks. The ophthalmic drops of the present invention should contain from 0.1-10% w/w of one of the compounds of Formula I. Typically, it will be dissolved in a buffered, isotonic solution containing antimicrobial preservative agents. The ophthalmic ointments will also generally contain from 0.1-10% w/w of one of the compounds of Formula I admixed with a suitable base, such as white petrolatum and mineral oil, along with antimicrobial preservatives. The ophthalmic disks will typically be constructed so as to contain a core of active ingredient surrounded by a polymer matrix such as, for example, a hydrophobic ethylene/vinyl acetate copolymer. Specific methods of compounding these dosage forms, as well as appropriate ophthalmic pharmaceutical carriers are known in the art. REMINGTON PHARMACEUTICALS SCIENCES, 16th Ed. Mack Publishing Co. (1980).

Typically, the ophthalmic drops or ophthalmic ointments will be administered from 1 to 4 times daily. The ophthalmic disks will be administered weekly.

WHAT IS CLAIMED IS:

1. Use of a compound of the formula:



in which R_1 and R_2 each independently are represented by hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen, nitro, hydroxy, SO_3H, SO_2NH_2, or R_1 and R_2 together may form a fused phenyl ring at the 1,2 or 3,4 positions, with the proviso that when R_1 and R_2 are identical, they represent hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, hydroxy, or halogen; A and B independently represent oxo, thio, or an imino group having the formula $-N(R_6)-$, wherein the group R_6 is represented by hydrogen or C_{1-4} alkyl; R_3 is hydrogen, C_{1-4} alkyl, or hydroxyethyl; n is represented by an integer from 2-5; and R_4 and R_5 are each represented by methyl or together form a cyclopentane or cyclohexane ring; the enantiomers thereof, and the pharmaceutically acceptable acid addition salts thereof, in the preparation of a medicament for the treatment of glaucoma.

2. Use according to claim 1 wherein said compound is 8-[2-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]-ethyl]-8-azaspiro[4,5]decane-7,9-dione.

3. Use according to claim 1 wherein said compound is 8-[2-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]butyl 1]-8-azaspiro[4,5]decane-7,9-dione.

4. A pharmaceutical composition suitable for ophthalmic administration comprising an effective amount of a compound of claim 1 in admixture with a suitable ophthalmic carrier.

5. A pharmaceutical composition according to claim 3 wherein said compound is 8-[2-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]ethyl]-8-azaspiro[4,5]decane-7,9-dione.

6. A pharmaceutical composition according to claim 3 wherein said compound is 8-[2-[[(2,3-dihydro-1,4-benzodioxin-2-yl)methyl]amino]butyl]-8-azaspiro[4,5]decane-7,9-dione.

7. A pharmaceutical composition according to claim 4 wherein said composition is opthalmic drops.

8. A pharmaceutical composition according to claim 4 wherein said composition is an opthalmic ointment.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/02994

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/445; A61K31/495; A61K31/535; A61K31/54

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category[o]	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 170 213 (MERRELL DOW) 5 February 1986 cited in the application & US,A,4 612 312 16 September 1986 see abstract; claims	1-8
A	EUROPEAN JOURNAL OF PHARMACOLOGY vol. 191, no. 3, 4 December 1990, pages 391 - 400; S.E. GARTSIDE ET AL.: 'EFFECTS OF MDL 73005EF ON CENTRAL PRE- AND POSTSYNAPTIC 5-HT1A RECEPTOR FUNCTION IN THE RAT IN VIVO' see the whole document	1-2,4-5

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[o] Special categories of cited documents :[10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03 SEPTEMBER 1992	21. 09. 92
International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer HOFF...

Form PCT/ISA/210 (second sheet) (January 1985)

Mme Dagmar FRANK

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	JOURNAL OF MEDICINAL CHEMISTRY vol. 31, 1988, pages 1087 - 1093; M.F. HIBERT ET AL.: 'GRAPHICS COMPUTER-AIDED RECEPTOR MAPPING AS A PREDICTIVE TOOL FOR DRUG DESIGN: DEVELOPMENT OF POTENT, SELECTIVE, AND STEREOSPECIFIC LIGANDS FOR THE 5-HT1A RECEPTOR' see the whole document	1,3-4,6
A	CHEMICAL ABSTRACTS, vol. 109, 1988, Columbus, Ohio, US; abstract no. 31918D, MIR A.K. ET AL.: 'MDL 72832: A POTENT AND STEREOSELECTIVE LIGAND AT CENTRAL AND PERIPHERAL 5-HT1A RECEPTORS' page 51 ; see abstract	1,3-4,6
A	CURRENT EYE RESEARCH vol. 6, no. 3, 1987, pages 527 - 532; P. MALLORGA ET AL.: 'CHARACTERIZATION OF SEROTONIN RECEPTOR IN THE IRIS + CILIARY BODY OF THE ALBINO RABBIT' see the whole document	1-8
A	EXP. EYE RES. vol. 44, no. 6, 1987, pages 731 - 746; N.N. OSBORNE ET AL.: 'SEROTONIN-ACCUMULATING CELLS IN THE IRIS-CILIARY BODY AND CORNEA OF VARIOUS SPECIES' see page 744	1-8
A	EXP. EYE RES. vol. 45, 1987, pages 721 - 729; K. KROOLITA ET AL.: 'EFFECT OF ALPHA-ADRENERGIC AND SEROTONIN BLOCKERS ON THE ACUTE IRRITATIVE RESPONSE IN THE RABBIT EYE' see the whole document	1-8
A	EP,A,0 329 903 (MERRELL DOW) 30 August 1989 see the whole document, esp. page 4, line 58-page 5, line 1	1-8

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9202994 SA 60506

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/09/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0170213	05-02-86	AU-B- 578962	10-11-88
		AU-A- 4535385	06-02-86
		CA-A- 1244418	08-11-88
		JP-A- 61246180	01-11-86
		US-A- 4612312	16-09-86
US-A-4612312	16-09-86	AU-B- 578962	10-11-88
		AU-A- 4535385	06-02-86
		CA-A- 1244418	08-11-88
		EP-A,B 0170213	05-02-86
		JP-A- 61246180	01-11-86
EP-A-0329903	30-08-89	AU-A- 3021489	24-08-89
		EP-A- 0329932	30-08-89
		JP-A- 2288880	28-11-90
		US-A- 5011846	30-04-91